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Synthesis of 3-(Trifluoromethyl)pyrazoles and Polysubstituted Pyrazoles by a *t*BuOK-Mediated Intramolecular Cyclization

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A highly efficient *t*BuOK-mediated synthesis of 3-(trifluoromethyl)pyrazoles and other polysubstituted pyrazoles by intramolecular cyclization of *N*-propargylhydrazones has been developed. This protocol provides an alternative route to 4-substituted 3-(trifluoromethyl)pyrazoles with good regioselectivity and shows good functional-group compatibility as well as high efficiency. Of note is the fact that the reactions on the gram scale also gave excellent yields.

Introduction

Compounds bearing CF_3 groups are absent in nature, but the introduction of trifluoromethyl groups into organic molecules can lead to profound changes in their biological properties.[1] Pyrazole bearing a 3-(trifluoromethyl) group is a distinguished example, and has proven to be the core unit of many commercial drugs and related candidates.[2,3] Representative examples of successfully commercialized pyrazoles bearing a 3-CF_3 group are shown in Figure 1. Celecoxib[2a] and Mavacoxib[2c] are selective COX-2 inhibitors, and Penthiopyrad[2b] is a fungicide.

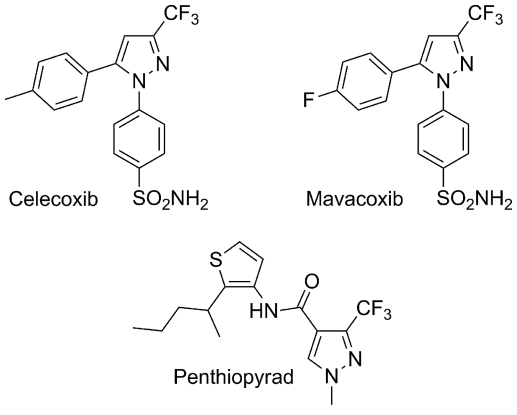
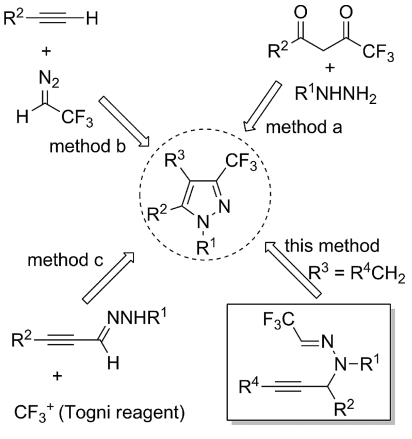


Figure 1. Selected examples of the polysubstituted pyrazole scaffold in natural products and bioactive molecules.

In recent years, tremendous efforts have been directed towards the development of efficient methods for the introduction of a CF_3 group at the 3-position of the pyrazole ring[4] or the construction of pyrazoles bearing a 3-CF_3 group.[5–7] Traditionally, 3-(trifluoromethyl)pyrazoles have been constructed by the cyclocondensation of an appropriate hydrazine with the corresponding 1,3-dielectrophilic compound,[5] especially with 1,3-dicarbonyl compounds (Scheme 1, method a). However, the drawback of this method is obvious, namely its poor regioselectivity. An alternative using a 1,3-dipolar cycloaddition strategy was reported by Ma and co-workers[6a] (Scheme 1, method b), but in this case 2 equiv. of Ag_2O were required. Moreover, 4-substituted pyrazoles cannot be synthesized by this reaction. Intramolecular cyclization is also a good method for the construction of 3-(trifluoromethyl)pyrazoles. The synthesis of 3-(trifluoromethyl)pyrazoles by trifluoromethylation/cyclization of α,β-alkynic hydrazones with the Togni reagent was reported by Wang and co-workers[7] (Scheme 1, method c). However, this method was also inefficient for the construction of 4-substituted 3-(trifluoromethyl)pyrazoles as only low to moderate yields were obtained.



Scheme 1. Synthesis of 3-trifluoromethylpyrazoles.

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Continuing our research into the reactions of propargylhydrazones,[8] we herein report the synthesis of 4-substituted 3-(trifluoromethyl)pyrazoles in extremely high yields from *N*-propargylhydrazones by a *t*BuOK-mediated intramolecular cyclization process under mild conditions (Scheme 1, this method).

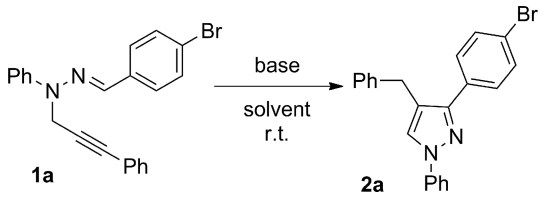
Results and Discussion

Substrate **1a** was chosen as the model substrate for our study, and some of the results are listed in Table 1. Initially, substrate **1a** was treated with a catalytic amount of DMAP[8b] [4-(dimethylamino)pyridine; 5 mol-%] in CH_3CN at room temperature (room temp.); however, this gave no product at all. The reaction performed at a higher temperature (80 °C) or with a high catalyst loading did not work (Table 1, Entries 1 and 2). Changing the solvent to DMF also led to no reaction (Table 1, Entry 3). We speculated that a stronger base may promote the reaction. With this in mind, we then tested a range of other bases, including K_2CO_3, Cs_2CO_3, and *t*BuOK, and found that the treatment of **1a** with Cs_2CO_3 did furnish the pyrazole **2a** in 91% yield within 3 h (Table 1, Entry 5). The structure of **2a** was unambiguously determined by a single-crystal X-ray structure analysis (Figure 2).[9] Further studies revealed that *t*BuOK was the best base for this transformation; it not only improved the yield of **2a** to 92%, but also dramatically shortened the reaction time (10 min; Table 1, Entry 6). Solvent screening revealed that the solvents DMSO, $PhCH_3$, CH_3NO_2, DCE, and 1,4-dioxane did not lead to any detectable product formation or decreased the yield (Table 1, Entries 7–11). In contrast, the use of CH_3CN as solvent increased the yield to 96% (Table 1, Entry 12). Moreover, it was found that the reaction mediated by 1.0 equiv. of *t*BuOK also gave a high yield (Table 1, entry 13). Hence, the optimal reaction conditions for this cyclization were determined to comprise 1 equiv. of *t*BuOK as base, CH_3CN as the solvent, and room temperature for 10 min.

3-(Trifluoromethyl)pyrazoles are the core structures of many bioactive molecules;[2,3] thus, we set out to synthesize these compounds by using the optimized reaction conditions (Scheme 2). The starting substrate bearing a phenyl group at the alkynyl position was first examined, and the targeted product **2b** was formed in good to excellent yields, although a longer reaction time (5 h) was required. Similarly, a substrate bearing the 2-naphthyl group at the alkynyl position also reacted smoothly to give **2c** in 93% yield. The pyrazoles **2d** and **2e** were also obtained in good yields. Pleasingly, the substrate bearing thiophene at the alkynyl position was also tolerated, and the corresponding pyrazole **2f** was obtained in 95% yield. In addition, an excellent yield was obtained with R^2 as an alkyl group (Scheme 2, product **2g**). Moreover, a terminal alkyne also reacted smoothly to give the desired pyrazole in 93% yield (Scheme 2, product **2h**).

We next evaluated the scope of the reaction under the optimal conditions by placing different substituents (R^1, R^2, R^3, R^4) at various positions of the *N*-propargylhydrazone **1** (Table 2). The alkynyl position R^2 was found to tolerate phenyl groups substituted with an electron-donating group (OMe; Table 2, Entry 2) as well as alkyl and heteroaryl substituents, for example butyl and 2-thienyl (Table 2, Entries 4 and 7). However, a phenyl group substituted with an electron-withdrawing group (NO_2) seemed to completely prevent the formation of pyrazole and led to a complex mixture (Table 2, Entry 3). Of note is the fact that a terminal alkyne also reacted to give the desired pyrazole

Table 1. Optimization of the reaction conditions for the synthesis of pyrazole **2a**.



Entry[a]	Base	Solvent	Time	Yield[b] [%]
1[c]	DMAP (5 mol-%)	CH_3CN	5 h	n.r.
2[c]	DMAP (1.5 equiv.)	CH_3CN	5 h	n.r.
3	DMAP (1.5 equiv.)	DMF	5 h	n.r.
4	K_2CO_3 (1.5 equiv.)	DMF	5 h	n.r.
5	Cs_2CO_3 (1.5 equiv.)	DMF	3 h	91
6	*t*BuOK (1.5 equiv.)	DMF	10 min	92
7	*t*BuOK (1.5 equiv.)	DMSO	10 min	67
8	*t*BuOK (1.5 equiv.)	$PhCH_3$	5 h	n.r.
9	*t*BuOK (1.5 equiv.)	CH_3NO_2	5 h	n.r.
10	*t*BuOK (1.5 equiv.)	DCE	5 h	n.r.
11	*t*BuOK (1.5 equiv.)	1,4-dioxane	5 h	n.r.
12	*t*BuOK (1.5 equiv.)	CH_3CN	10 min	96
13	*t*BuOK (1.0 equiv.)	CH_3CN	10 min	99

[a] Reaction conditions: **1a** (0.2 mmol), solvent (3 mL). [b] Isolated yield. n.r. = no reaction. [c] Reaction temperature was in the range from room temp. to 80 °C.

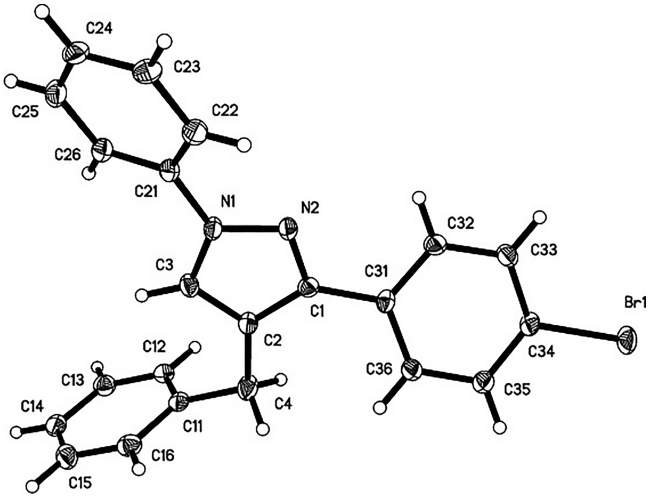
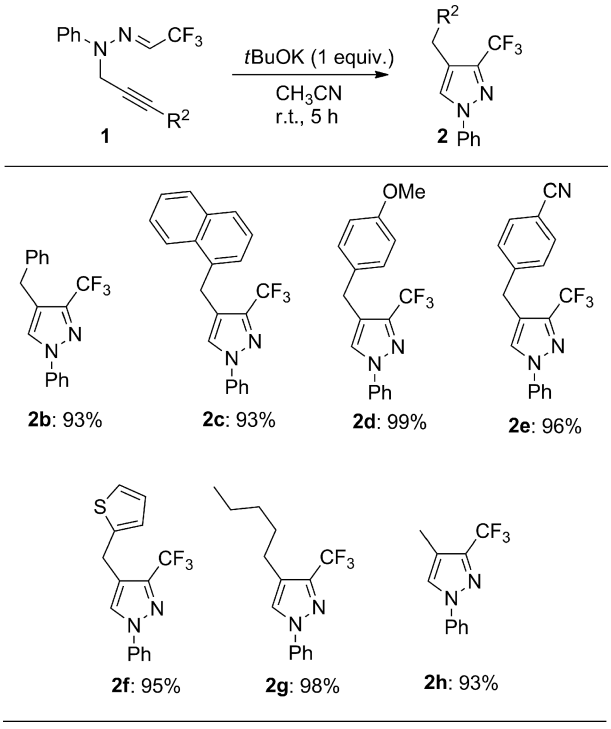


Figure 2. X-ray crystal structure of product **2a** (ellipsoids are drawn at the 30% probability level).



Scheme 2. Synthesis of 4-substituted 3-(trifluoromethyl)pyrazoles. Reaction conditions: **1** (0.2 mmol), CH_3CN (3 mL), in Schlenk tube; isolated yields.

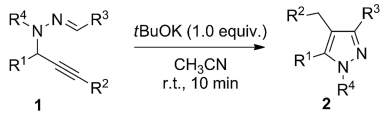
in 94% yield (Table 2, Entry 5). The introduction of the trimethylsilyl (TMS) group led to the formation of a product resulting from TMS extrusion (Table 2, Entry 6).

Hydrazones derived from heteroaryl (including 2-thienyl and 2-furyl) aldehydes were also found to be suitable substrates for this transformation (Table 2, products **2o**, **2p**, and **2t**). With R^3 as 1-naphthyl and styrenyl, the corresponding pyrazoles were formed in yields of 94 and 99%, respectively (Table 2, Entries 10 and 12). Moreover, a hydrazone derived from an alkyl aldehyde also gave an excellent yield (Table 2, Entry 11). Meanwhile, branching at the propargylic position was also tolerated (R^1 = *n*-pentyl) and the desired pyrazole was obtained in 97% yield (Table 2, Entry 14). Additionally, replacing the R^4 phenyl group by a cyclohexyl ring also gave the desired product in 94% yield (Table 2, Entry 15).

We previously reported the conversion of *N*-Ts-propargylhydrazones into allenic hydrazones.[8b] Based on the above results and those of our previous investigations, the pathway for the formation of **2** is considered to proceed as illustrated in Scheme 3. The reaction possibly starts with the isomerization of the propargylhydrazone **1** to the allenic compound **A** mediated by *t*BuOK. The subsequent cyclization of **A** is expected to provide intermediate **B**, which undergoes auto-isomerization to give the desired product **2**.

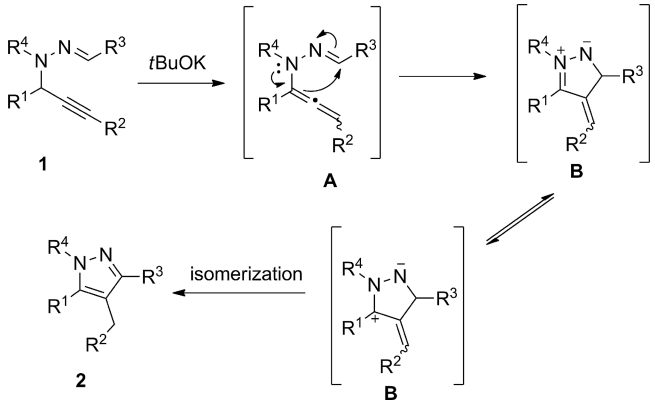
To illustrate the practicability of this method, two reactions were carried out on the gram scale (Scheme 4). Substrate **1b** bearing a CF_3 group at the 3-position was examined, and the desired product **2b** was formed in 91% yield [Scheme 4 (a)]. This is a yield similar to that obtained with the same substrate in Scheme 2, which reveals that this is a highly efficient preparative method. Moreover, propargylic hydrazone **1l** could also be converted into the corresponding pyrazole **2l** in 91% yield on the gram scale [Scheme 4 (b)].

Table 2. Synthesis of polysubstituted pyrazoles.

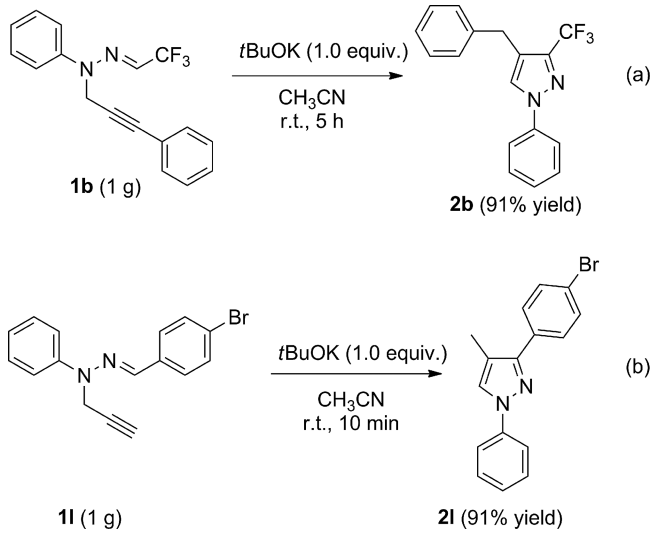


Entry[a]	Substrate	Procduct	Yield [%][b]
1	**1a** (R^2 = Ph)		99 (**2a**)
2	**1i** (R^2 = *p*-MeOC$_6$H$_4$)		97 (**2i**)
3	**1j** (R^2 = *p*-O$_2$NC$_6$H$_4$)		complex
4	**1k** (R^2 = butyl)		90 (**2k**)
5	**1l** (R^2 = H)		94 (**2l**)
6	**1m** (R^2 = TMS)		81 (**2l**)
7	**1n** (R^2 = 2-thienyl)		99 (**2n**)
8	**1o** (R^3 = 2-thienyl)		96 (**2o**)
9	**1p** (R^3 = 2-furyl)		97 (**2p**)
10	**1q** (R^3 = 1-naphthyl)		94 (**2q**)
11	**1r** (R^3 = *n*-pentyl)		95 (**2r**)
12	**1s** (R^3 = styrenyl)		99 (**2s**)
13	**1t**		90 (**2t**)
14	**1u** (R^1 = *n*-pentyl)		97 (**2u**)
15	**1v** (R^4 = cyclohexyl, R^3 = Ph)		94 (**2v**)

[a] Reaction conditions: **1** (0.2 mmol), CH_3CN (3 mL), in Schlenk tube. [b] Isolated yields.



Scheme 3. Plausible reaction mechanism for the formation of **2**.



Scheme 4. Two reactions carried out on the gram scale.

Conclusions

We have reported a highly efficient method for the synthesis of 4-substituted 3-(trifluoromethyl)pyrazoles and other 4-substituted pyrazoles from *N*-propargylhydrazones by a *t*BuOK-mediated intramolecular cyclization process. The method is applicable to a wide range of substrates, thus providing a convenient access to a variety of highly functionalized pyrazoles. Of note is the fact that the reactions also gave excellent yields on the gram scale.

Experimental Section

General: All the solvents were freshly distilled prior to use. All reaction mixtures were stirred with a magnetic bar in flame-dried glassware. Column chromatography on silica gel (300–400 mesh) or Al_2O_3 (200–300 mesh) was carried out by using technical-grade petroleum ether (boiling range 60–90 °C) (distilled prior to use) and analytical-grade EtOAc (without further purification). ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 400/100/376 MHz or 500/125 MHz spectrometer by using $CDCl_3$ or $(CD_3)_2SO$ as solvent and TMS as internal standard. ^{19}F NMR spectra were recorded with a Bruker Avance 376 MHz spectrometer by using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are reported in ppm. IR spectra were recorded with a Nicolet Avatar 360 FT-IR spectrometer as thin films on KBr wafers. Mass spectra were recorded with an En Apex Ultra 7.0 FT-MS high-resolution mass spectrometer. Melting point were recorded with a Yanaco MP-500 melting point apparatus.

General Experimental Procedures for the Preparation of Polysubstituted Pyrazoles 2: The corresponding propargylhydrazone **1** (50 mg) and *t*BuOK (1.0 equiv.) were placed in a 10 mL Schlenk tube followed by the addition of CH_3CN (3 mL). The reaction mixture was then stirred at room temp. under N_2. Upon completion of the reaction (monitored by TLC), the solvent was removed under vacuum, and the crude residue was purified by silica gel column chromatography to afford the corresponding pyrazoles **2** (eluent: petroleum ether/EtOAc, 100:1).

4-Benzyl-3-(4-bromophenyl)-1-phenyl-1*H*-pyrazole (2a): White solid (49.4 mg; m.p. 140–142 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.00 (s, 2 H), 7.18–7.26 (m, 4 H), 7.27–7.33 (m, 2 H), 7.36–7.43 (m, 2 H), 7.48–7.54 (m, 2 H), 7.56–7.59 (m, 2 H), 7.59–7.62 (m, 1 H), 7.64–7.67 (m, 1 H), 7.67–7.70 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0, 118.8, 120.4, 122.0, 126.3, 126.4, 127.8, 128.6, 128.7, 129.4, 131.7, 132.5, 140.0, 140.2, 150.4 ppm. IR (film): $\tilde{\nu}$ = 3060, 2920, 1600, 1502, 756 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{18}BrN_2^+$ $[M + H]^+$ 389.0648, 391.0628; found 389.0642, 391.0621.

4-Benzyl-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole (2b): Light-yellow liquid (46.7 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.00 (s, 2 H), 7.26–7.32 (m, 3 H), 7.32–7.40 (m, 3 H), 7.41–7.48 (m, 2 H), 7.54 (s, 1 H), 7.60–7.66 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6, 119.5, 121.77 (q, J = 268.0 Hz), 121.80, 126.6, 127.4, 128.0, 128.6, 128.7, 129.4, 139.2, 139.3, 141.3 (q, J = 36.4 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –60.91 ppm. IR (film): $\tilde{\nu}$ = 3064, 2925, 1601, 1493, 757.4 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{14}F_3N_2^+$ $[M + H]^+$ 303.1104; found 303.1101.

4-(1-Naphthylmethyl)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole (2c): Viscous liquid (46.7 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.38 (s, 2 H), 7.15–7.23 (m, 2 H), 7.25–7.32 (m, 2 H), 7.33–7.38 (m,1 H), 7.39–7.50 (m, 5 H), 7.75–7.82 (m, 1 H), 7.83–7.89 (m, 1 H), 7.89–7.97 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.2, 119.4, 121.5, 121.9 (q, J = 267.6 Hz), 123.9, 125.6, 125.8, 126.3, 127.0, 127.3, 127.7, 128.1, 128.8, 129.3, 131.6, 134.0, 134.9, 139.2, 141.1 (q, J = 35.8 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –60.92 ppm. IR (film): $\tilde{\nu}$ = 3063, 2951, 1600, 1498, 781 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{16}F_3N_2^+$ $[M + H]^+$ 353.1261; found 353.1260.

4-(4-Methoxybenzyl)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole (2d): Light-yellow liquid (49.5 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 3.93 (s, 2 H), 6.87–6.92 (m, 2 H), 7.15–7.21 (m, 2 H), 7.29–7.35 (m, 1 H), 7.40–7.46 (m, 2 H), 7.50–7.53 (m, 1 H), 7.60–7.65 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7, 55.2, 114.1, 119.5, 121.8 (q, J = 214.4 Hz), 122.4, 127.4, 127.9, 129.4, 129.6, 131.3, 139.3, 141.2 (q, J = 29.2 Hz), 158.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –60.94 ppm. IR (film): $\tilde{\nu}$ = 3053, 2934, 2837, 1600, 1505, 756 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{16}F_3N_2O^+$ $[M + H]^+$ 333.1209; found 333.1214.

4-{[1-Phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl}benzonitrile (2e): Light-yellow solid (47.8 mg; m.p. 94–95 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.05 (s, 2 H), 7.31–7.37 (m, 3 H), 7.42–7.48 (m, 2 H), 7.58–7.61 (m, 1 H), 7.61–7.64 (m, 3 H), 7.64–7.67 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.7, 110.7, 118.7, 119.6, 119.7, 121.6 (q, J = 268.1 Hz), 127.8, 128.0, 129.4, 129.6, 132.5, 139.2, 141.5 (q, J = 6.6 Hz), 144.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –60.87 ppm. IR (film): $\tilde{\nu}$ = 3068, 2954, 1602, 1498 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{13}F_3N_3^+$ $[M + H]^+$ 328.1057; found 328.1061.

1-Phenyl-4-(thiophen-2-ylmethyl)-3-(trifluoromethyl)-1*H*-pyrazole (2f): Light-yellow liquid (47.6 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.20 (s, 2 H), 6.90–6.95 (m, 1 H), 6.96–7.01 (m, 1 H), 7.18–7.24 (m, 1 H), 7.30–7.38 (m, 1 H), 7.41–7.50 (m, 2 H), 7.62–7.69 (m, 2 H), 7.71 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 119.6, 121.3, 121.7 (q, J = 268.0 Hz), 124.2, 125.6, 127.0, 127.6, 128.1, 129.5, 139.3, 141.1 (q, J = 36.8 Hz), 141.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –60.92 ppm. IR (film): $\tilde{\nu}$ = 3072, 2925, 1600, 1493, 758 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{12}F_3N_2S^+$ $[M + H]^+$ 309.0668; found 309.0667.

4-Pentyl-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole (2g): Light-yellow liquid (49.1 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, J

= 6.9 Hz, 3 H), 1.33–1.44 (m, 4 H), 1.60–1.70 (m, 2 H), 2.62 (t, *J* = 7.7 Hz, 2 H), 7.27–7.37 (m, 1 H), 7.40–7.50 (m, 2 H), 7.63–7.71 (m, 2 H), 7.75 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 23.2, 29.9, 31.4, 119.4, 121.9 (q, *J* = 268.0 Hz), 122.7, 126.9, 127.3, 129.5, 139.5, 141.5 (q, *J* = 36.3 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.05 ppm. IR (film): $\tilde{\nu}$ = 3053, 2932, 1602, 1492, 757 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{18}F_3N_2^+$ [M + H]$^+$ 283.1417; found 283.1410.

4-Methyl-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole (2h): Light-yellow liquid (46.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 7.28–7.37 (m, 1 H), 7.40–7.50 (m, 2 H), 7.60–7.70 (m, 2 H), 7.72 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.1, 117.1, 119.4, 121.9 (q, *J* = 214.0 Hz), 127.3, 127.6, 129.5, 139.4, 142.1 (q, *J* = 29.0 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.51 ppm. IR (film): $\tilde{\nu}$ = 3053, 2963, 1601, 1495, 1392 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{10}F_3N_2^+$ [M + H]$^+$ 227.0791; found 227.0795.

3-(4-Bromophenyl)-4-(4-methoxybenzyl)-1-phenyl-1*H*-pyrazole (2i): Light-yellow solid (48.6 mg; m.p. 104–106 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 3.98 (s, 2 H), 6.84–6.92 (m, 2 H), 7.12–7.20 (m, 2 H), 7.24–7.30 (m, 1 H), 7.40–7.48 (m, 2 H), 7.52–7.58 (m, 2 H), 7.58–7.66 (m, 3 H), 7.68–7.74 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2, 55.3, 114.1, 118.8. 121.0, 122.0, 126.3, 127.7, 129.38, 129.41, 129.5, 131.6, 132.2, 132.5, 140.0, 150.2, 158.2 ppm. IR (film): $\tilde{\nu}$ = 3051, 2928, 2834, 1600, 1503, 755 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{20}BrN_2O^+$ [M + H]$^+$ 419.0754, 421.0734; found 419.0751, 421.0730.

3-(4-Bromophenyl)-4-pentyl-1-phenyl-1*H*-pyrazole (2k): Light-yellow solid (45.1 mg; m.p. 74–76 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (s, 3 H), 1.33–1.43 (m, 4 H), 1.60–1.72 (m, 2 H), 2.66 (t, *J* = 7.6 Hz, 2 H), 7.23–7.32 (m, 1 H), 7.40–7.50 (m, 2 H), 7.54–7.62 (m, 2 H), 7.62–7.70 (m, 2 H), 7.70–7.77 (m, 2 H), 7.78 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.5, 24.8, 29.7, 29.9, 31.7, 118.7, 121.7, 122.0, 126.1, 126.3, 129.37, 129.40, 131.6, 132.9, 140.1, 150.2 ppm. IR (film): $\tilde{\nu}$ = 3051, 2928, 2857, 1600, 1502, 755 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{22}BrN_2^+$ [M + H]$^+$ 369.0961, 371.0941; found 369.0968, 371.0947.

3-(4-Bromophenyl)-4-methyl-1-phenyl-1*H*-pyrazole (2l): Light-yellow solid (47.2 mg; m.p. 79–80 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 7.24–7.30 (m, 1 H), 7.40–7.48 (m, 2 H), 7.55–7.61 (m, 2 H), 7.66–7.74 (m, 4 H), 7.75–7.79 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.3, 116.2, 118.7, 121.6, 126.1, 127.2, 129.0, 129.4, 131.5, 132.7, 140.0, 150.4 ppm. IR (film): $\tilde{\nu}$ = 3051, 2925, 1599, 1503, 755 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{14}BrN_2^+$ [M + H]$^+$ 313.0335, 315.0315; found 313.0333, 315.0312.

3-(4-Bromophenyl)-1-phenyl-4-(thiophen-2-ylmethyl)-1*H*-pyrazole (2n): Llight-yellow solid (49.6 mg; m.p. 133–134 °C). ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ = 4.24 (s, 2 H), 6.84–6.88 (m, 1 H), 6.90–6.95 (m, 1 H), 7.27–7.35 (m, 2 H), 7.46–7.53 (m, 2 H), 7.57–7.63 (m, 2 H), 7.63–7.69 (m, 2 H), 7.84–7.90 (m, 2 H), 8.46 (s, 1 H) ppm. ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ = 25.0, 118.6, 120.1, 121.7, 124.7, 125.5, 126.8, 127.5, 129.3, 129.7, 130.0, 132.0, 132.6, 139.8, 144.0, 149.5 ppm. IR (film): $\tilde{\nu}$ = 3068, 2922, 1600, 1502, 755 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{16}BrN_2S^+$ [M + H]$^+$ 395.0213, 397.0192; found 395.0210, 397.0190.

4-Benzyl-1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole (2o): Light-yellow solid (47.8 mg; m.p. 112–113 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.11 (s, 2 H), 7.05–7.13 (m, 1 H), 7.24–7.39 (m, 8 H), 7.40–7.47 (m, 2 H), 7.56 (s, 1 H), 7.66–7.75 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9, 118.6, 120.0, 125.00, 125.03, 126.1, 126.3, 127.4, 127.5, 128.6, 129.3, 135.8, 139.7, 146.2 ppm. IR (film): $\tilde{\nu}$ = 3061, 2920, 1599, 1503, 756 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{17}N_2S^+$ [M + H]$^+$ 317.1107; found 317.1111.

4-Benzyl-3-(furan-2-yl)-1-phenyl-1*H*-pyrazole (2p): Yellow solid (48.6 mg; m.p. 45–47 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.08 (s, 2 H), 6.46 (dd, *J* = 3.4, 1.8 Hz, 1 H), 6.65 (d, *J* = 3.2 Hz, 1 H), 7.20–7.28 (m, 4 H), 7.28–7.33 (m, 2 H), 7.36–7.41 (m, 2 H), 7.47–7.57 (m, 2 H), 7.63–7.68 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.7, 107.5, 111.2, 118.9, 120.4, 126.2, 126.3, 127.2, 128.5, 128.6, 129.2, 139.8, 140.0, 142.1, 143.3, 148.4 ppm. IR (film): $\tilde{\nu}$ = 3061, 2923, 1599, 1503, 756 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{17}N_2O^+$ [M + H]$^+$ 301.1336; found 301.1334.

4-Benzyl-3-(1-naphthyl)-1-phenyl-1*H*-pyrazole (2q): Yellow liquid (47.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 2 H), 7.05–7.18 (m, 3 H), 7.18–7.27 (m, 3 H), 7.37–7.44 (m, 2 H), 7.45–7.57 (m, 4 H), 7.70–7.78 (m, 3 H), 7.86–7.94 (m, 2 H), 7.98–8.08 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.6, 118.7, 122.7, 125.2, 125.8, 126.0, 126.1(8), 126.2(3), 126.3, 128.1, 128.2, 128.4, 128.5, 128.6, 129.3, 130.7, 132.4, 133.8, 140.1, 140.6, 151.5 ppm. IR (film): $\tilde{\nu}$ = 3052, 2923, 1600, 1504, 756 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{21}N_2^+$ [M + H]$^+$ 361.1700; found 361.1694.

4-Benzyl-3-pentyl-1-phenyl-1*H*-pyrazole (2r): Light-yellow liquid (47.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7 Hz, 3 H), 1.28–1.38 (m, 4 H), 1.58–1.68 (m, 2 H), 2.60 (t, *J* = 7.8 Hz, 2 H), 3.83 (s, 2 H), 7.15–7.25 (m, 4 H), 7.26–7.33 (m, 2 H), 7.34–7.41 (m, 2 H), 7.51 (s, 1 H), 7.56–7.63 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.5, 26.8, 28.9, 30.1, 31.8, 118.4, 120.3, 125.5, 126.1, 128.4, 128.5, 129.2, 140.2, 140.5, 153.5 ppm. IR (film): $\tilde{\nu}$ = 3027, 2928, 1600, 1504, 754 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{25}N_2^+$ [M + H]$^+$ 305.2013; found 305.2011.

(*E*)-4-Benzyl-1-phenyl-3-styryl-1*H*-pyrazole (2s): Light-yellow solid (47.8 mg; m.p. 111–113 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 2 H), 7.98–7.05 (m, 1 H), 7.10–7.21 (m, 5 H), 7.21–7.29 (m, 5 H), 7.29–7.36 (m, 2 H), 7.36–7.42 (m, 2 H), 7.46 (s, 1 H), 7.55–7.63 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.5, 118.7, 121.3, 126.1, 126.3, 126.5, 127.0, 127.6, 128.5, 128.58, 128.61, 129.3, 130.6, 137.3, 139.9(4), 139.9(8), 149.2 ppm. IR (film): $\tilde{\nu}$ = 3025, 2923, 1599, 1503, 754 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{21}N_2^+$ [M + H]$^+$ 337.1700; found 337.1696.

3-(Furan-2-yl)-4-methyl-1-phenyl-1*H*-pyrazole (2t): Light-yellow solid (44.8 mg; m.p. 70–71 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 6.48–6.51 (m, 1 H), 6.68–6.71 (m, 1 H), 7.21–7.26 (m, 1 H), 7.37–7.44 (m, 2 H), 7.50–7.53 (m, 1 H), 7.66–7.72 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.7, 107.2, 111.1, 116.0, 118.8, 126.0, 126.7, 129.2, 139.9, 141.9, 143.8, 148.7 ppm. IR (film): $\tilde{\nu}$ = 3058, 2921, 1601, 1497, 773 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{13}N_2O^+$ [M + H]$^+$ 225.1023; found 225.1021.

4-Benzyl-3-(4-bromophenyl)-5-pentyl-1-phenyl-1*H*-pyrazole (2u): Yellow liquid (48.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 6.8 Hz, 3 H), 1.08–1.16 (m, 4 H), 1.28–1.36 (m, 2 H), 2.60 (t, *J* = 8.0 Hz, 2 H), 4.04 (s, 2 H), 7.16–7.25 (m, 3 H), 7.27–7.33 (m, 2 H), 7.40–7.48 (m, 3 H), 7.49–7.57 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 21.9, 24.6, 28.4, 29.6, 31.3, 114.5, 121.6, 125.7, 126.0, 127.96, 128.03, 128.4, 129.1, 129.4, 131.4, 132.7, 140.1, 140.5, 143.3, 150.1 ppm. IR (film): $\tilde{\nu}$ = 3061, 2955, 2927, 1598, 1500, 1365, 729 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{28}BrN_2^+$ [M + H]$^+$ 459.1431, 461.1410; found 459.1428, 461.1405.

4-Benzyl-1-cyclohexyl-3-phenyl-1*H*-pyrazole (2v): Light-yellow solid (47.1 mg; m.p. 109–111 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20–1.33 (m, 2 H), 1.38–1.49 (m, 2 H), 1.68–1.78 (m, 2 H), 1.86–1.94 (m, 2 H), 2.17–2.24 (m, 2 H), 4.0 (s, 2 H), 4.11 (tt, *J* = 11.8, 3.8 Hz, 1 H), 7.11 (s, 1 H), 7.19–7.25 (m, 3 H), 7.28–7.34 (m, 3 H), 7.37–7.42 (m, 2 H), 7.62–7.68 (m, 2 H) ppm. ^{13}C NMR (125 MHz,

$CDCl_3$): δ = 25.3, 25.4, 30.9, 33.6, 61.2, 117.1, 126.0, 127.1, 127.2, 127.7, 128.3, 128.4, 128.5, 134.2, 141.1, 148.8 ppm. IR (film): $\tilde{\nu}$ = 3060, 2929, 1602, 1494, 770 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{25}N_2^+$ $[M + H]^+$ 317.2013; found 317.2015.

Experimental Procedures for the Preparation of Polysubstituted Pyrazole 2l on the Gram Scale: The corresponding hydrazone (2.0 g, 7.27 mmol) and Cs_2CO_3 (8.84 g, 8.72 mmol) were placed in an oven-dried round-bottomed flask, and then DMF (35 mL) was added. Finally, the corresponding propargyl bromide (1.04 g, 8.72 mmol) was added under N_2, and the reaction mixture was stirred at room temperature. Upon completion (monitored by TLC), the mixture was diluted with water (150 mL), and the aqueous phase was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried with Na_2SO_4. The solvent was removed under vacuum, and the crude residue was purified by recrystallization (hexane/MeOH, 100:1) to afford the corresponding the propargylhydrazone **1l** (1.48 g, 65% yield). *t*BuOK (358 mg, 3.2 mmol) was placed in a 150 mL three-necked bottle followed by the addition of CH_3CN (70 mL) and substrate **1l** (1 g, 3.2 mmol), dissolved in CH_3CN (15 mL) under N_2. The reaction mixture was stirred at room temp. Upon completion (monitored by TLC), the solvent was removed under vacuum and the crude residue purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 100:1) to afford the corresponding pyrazole **2l** (0.908 g, 91% yield).

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[9] CCDC-1046486 (for **2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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